

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
29 March 2001 (29.03.2001)

PCT

(10) International Publication Number
WO 01/21765 A3

- (51) International Patent Classification⁷: C12N 5/06, A61K 31/40, 38/04, C12Q 1/02, A61P 35/00 (74) Agents: LEONE, Mario et al.; Società Italiana Brevetti S.p.A., Piazza di Pietra, 39, I-00186 Roma (IT).
- (21) International Application Number: PCT/IT00/00373 (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (22) International Filing Date: 21 September 2000 (21.09.2000)
- (25) Filing Language: English
- (26) Publication Language: English (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- (30) Priority Data: RM99A000580 21 September 1999 (21.09.1999) IT
- (71) Applicant (*for all designated States except US*): UNIVERSITA' DEGLI STUDI DI ROMA "LA SAPIENZA" [IT/IT]; Piazzale Aldo Moro, 5, I-00185 Roma (IT).
- Published:
— with international search report
- (72) Inventors; and (88) Date of publication of the international search report:
11 October 2001
- (75) Inventors/Applicants (*for US only*): TATO', Franco [IT/IT]; Via Oriolo Romano, 93, I-00189 Roma (IT). ZANETTI, Antonio [IT/IT]; Vicolo Vicinale, 5/8, I-00152 Roma (IT). GROSSI, Milena [IT/IT]; Via Raffaele Battistini, 90, I-00151 Roma (IT).
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: METHOD FOR THE SELECTIVE PROTECTION OF PROLIFERATING NORMAL CELLS AND THE SELECTIVE ERADICATION OF TUMOR CELLS HAVING AN INACTIVE p53 PATHWAY

(57) Abstract: Object of the present invention is a method for obtaining the selective protection of normal cells and, at the same time, the selective eradication of tumor cells having an inactive p53 pathway. Further objects of the present invention are the uses of the compounds of the method, pharmaceutical compositions and kits, comprising such compounds as active principles, and use of the C3H10T1/2 cells for implementing methods for the eradication of tumor cells having an inactive p53 pathway.

WO 01/21765 A3

INTERNATIONAL SEARCH REPORT

Internal : Application No

PCT/IT 00/00373

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N5/06 A61K31/40 A61K38/04 C12Q1/02 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, EPO-Internal, PAJ, WPI Data, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>RICHMAN C M ET AL: "INTERFERON PROTECTS NORMAL HUMAN GRANULOCYTE-MACROPHAGE COLONY-FORMING CELLS FROM ARA-C CYTOTOXICITY" JOURNAL OF BIOLOGICAL RESPONSE MODIFIERS, vol. 9, no. 6, 1990, pages 570-575, XP002165025 ISSN: 0732-6580 abstract page 570, column 2, last paragraph -page 571, column 1, paragraph 1 page 572, column 1 -column 2, paragraph 1 page 573, paragraph 3</p> <p>---</p>	<p>1-3, 10-12, 17,18, 24-27,30</p>
X A	<p>EP 0 297 946 A (UNIV SYRACUSE) 4 January 1989 (1989-01-04) abstract page 4, line 25 - line 42</p> <p>---</p> <p>-/--</p>	<p>17-23</p>

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

11 April 2001

Date of mailing of the international search report

04/05/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Noë, V

INTERNATIONAL SEARCH REPORT

Internat

Application No

PCT/IT 00/00373

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SASSE FLORENZ ET AL: "The chondramides: Cytostatic agents from myxobacteria acting on the actin cytoskeleton." JOURNAL OF THE NATIONAL CANCER INSTITUTE (BETHESDA), vol. 90, no. 20, 21 October 1998 (1998-10-21), pages 1559-1563, XP000990945 ISSN: 0027-8874	17-23
A	the whole document	
X	WO 97 10242 A (PHARMA MAR SA ;RUFFLES GRAHAM KEITH (GB); HIGA TATSUO (JP); TANAKA) 20 March 1997 (1997-03-20)	17-23
A	abstract page 1, paragraph 2 - last line page 2, last paragraph -page 3, paragraph 1 page 3, last paragraph -page 4, paragraph 1	
A	BOKEMEYER C ET AL: "SILIBININ PROTECTS AGAINST CISPLATIN-INDUCED NEPHROTOXICITY WITHOUT COMPROMISING CISPLATIN OR IFOSFAMIDE ANTI-TUMOUR ACTIVITY" BRITISH JOURNAL OF CANCER,GB,LONDON, vol. 74, 1996, pages 2036-2041, XP000874389 ISSN: 0007-0920 the whole document	
A	OTSUKA H ET AL: "VARIANT LINES OF MOUSE KIDNEY CELLS TRANSFORMED BY AN SV-40-TSA MUTANT WITH GROWTH PROPERTIES OF WILD TYPE TRANSFORMED CELLS AT NONPERMISSIVE TEMPERATURE" JOURNAL OF GENERAL VIROLOGY, vol. 42, no. 2, 1979, pages 373-386, XP000990951 EN ISSN: 0022-1317 abstract page 377, last paragraph -page 378, paragraph 1; figure 4	
A	RUBTSOVA S N ET AL: "Disruption of actin microfilaments by cytochalasin D leads to activation of p53." FEBS LETTERS, vol. 430, no. 3, 3 July 1998 (1998-07-03), pages 353-357, XP002164902 ISSN: 0014-5793 the whole document	

-/--

INTERNATIONAL SEARCH REPORT

Internat

I Application No

PCT/IT 00/00373

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WANG E A ET AL: "BONE MORPHOGENETIC PROTEIN-2 CAUSES COMMITMENT AND DIFFERENTIATION IN C3H10T1/2 AND 3T3 CELLS" GROWTH FACTORS, HARWOOD ACADEMIC PUBLISHERS GMBH, XX, vol. 9, no. 1, 1993, pages 57-71, XP002920878 ISSN: 0897-7194 abstract</p> <p>-----</p>	31-33

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-7,12-21,24,27-30 relate to a compositions, kits and methods having or using compounds defined by reference to a desirable characteristic or property, namely (a) chemotherapeutic compounds (in claim 3 also called class B compounds) said compounds exerting cytotoxic action toward actively proliferation cells and not affecting survival and proliferative potential of interphase cells and (b) protective compounds (in claim 3 also called A compounds) said compounds having the capability of reversibly inhibiting cytodieresis of normal cells and non-inhibiting the biological action of a chemotherapeutic compound. The claims cover all compositions, kits and methods having or using these compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds and methods. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound and their methods of use by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to compositions, kits and methods having or using the compounds described in claims 8-11, 22-23 and 25-26 and the general concept of the application, concerning the compositions, kits and methods in so far the compounds are defined as above in (a) and (b).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat: I Application No

PCT/IT 00/00373

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0297946 A	04-01-1989	AU 1969388 A JP 3500166 T WO 8810259 A	19-01-1989 17-01-1991 29-12-1988
WO 9710242 A	20-03-1997	AU 6936596 A	01-04-1997